The ascending aorta with bicuspid aortic valve: a phenotypic classification with potential prognostic significance†

Alessandro Della Corte*, Ciro Bancone, Giovanni Dialetto, Franco E. Covino, Sabrina Manduca, Marco V. Montibello, Marisa De Feo, Marianna Buonocore and Gianantonio Nappi

Department of Cardiothoracic Sciences, Second University of Naples, V. Monaldi Hospital, Naples, Italy

*Corresponding author. Department of Cardiothoracic Sciences, Second University of Naples, Cardiovascular Surgery and Transplant, V. Monaldi Hospital, via L Bianchi, 80131 Naples, Italy. Tel: +39-081-7064020; fax: +39-081-5464594; e-mail: aledellacorte@libero.it (A. Della Corte).

Received 12 September 2013; received in revised form 21 November 2013; accepted 28 November 2013

Abstract

OBJECTIVES: Different methods to classify the anatomical configurations of the aorta with bicuspid aortic valve (BAV) have been proposed. We aimed to test them in terms of descriptive power (i.e. capability to identify different clusters of patients with unique associations of anatomo-clinical features) and possible prognostic significance.

METHODS: A consecutive echocardiographic series of 696 BAV patients (mean age 48 ± 16 years, male:female ratio 3:1) was analysed. Three possible schemes for classification of the patterns of aortic dimensions were compared. One defined the aortic shape as ‘N’ (ascending < sinuses > sinotubular junction (STJ)), ‘A’ (ascending > sinuses > STJ) or ‘E’ (sinotubular > sinuses), the second as ‘non-dilated,’ ‘ascending phenotype’ (dilated, with ascending > sinuses) or ‘root phenotype’ (dilated with sinuses > ascending) and the third as normal, ‘type I’ (dilated only at the ascending) tract, ‘type II’ (dilated at both ascending and sinus levels) or ‘type III’ (dilated only at the sinuses). We evaluated the correlation with valve morphotypes (right-left fusion, right-non-coronary fusion) and patient characteristics. In a smaller longitudinal study (n = 150), the occurrence of fast growth of the aorta (fifth quintile: ≥1 mm/year) during follow-up (5 ± 3 years) in the various phenotypes was assessed.

RESULTS: The three classification methods proved meaningful in terms of association with valve morphotypes: significant associations were found between right-left-coronary BAV and the root phenotype (P < 0.001) and between the right-non-coronary BAV and the shapes A and E (P<0.001) as well as type I aortic configuration (P < 0.001). The aortic shape showed significant association with five of the other tested clinical variables, the phenotype and the type of dilatation with eight. In the longitudinal study, the root phenotype showed the most significant association with fast growth (>1 mm/year) of the ascending diameter (50% root phenotype patients; P = 0.005). The association with the N type was weaker (P = 0.055); no association was found with types from the other classification scheme (P = 0.42).

CONCLUSIONS: When tested on a large population, three previously suggested phenotypic classifications of the BAV aorta proved to categorize patients into significantly different clusters, but only the classification system distinguishing between ascending phenotype and root phenotype showed a potential prognostic value. Phenotypic class of the aorta could be a factor to integrate in future comprehensive models for risk stratification of BAV aortopathy.

Keywords: Bicuspid aortic valve • Aorta • Aortic dilatation • Classification • Prognosis • Echocardiography

INTRODUCTION

Bicuspid aortic valve (BAV), with its inherent increased risk of aortopathy, has long been an object of intensive clinical and basic research. Besides its epidemiological relevance (1–2% of all live births, responsible for ~50% of the aortic valve stenosis cases requiring surgery [1]), other characteristics of the BAV aortopathy that can account for the increasing interest in it include the relative unpredictability of its natural history, the persisting unknowns on the causative mechanisms and the heterogeneity of the anatomo-clinical forms that it can assume [1–4]. In particular, the variability in valve morphology and in phenotypic expression of the aortopathy is believed to likely account for the inconsistent findings both in studies of clinical outcomes and among investigations on the pathogenetic processes underlying dilatation [5, 6]. This calls for a standardization of the language used to indicate the variable phenotypes of BAV-related disease, which would allow more precise selection of study populations and comparability between analysis reports by different Authors. Furthermore, there is a clear need for prognostic stratification criteria in BAV aortopathy, as the diameter of the aorta seems a poor risk marker for aortic events and it does not necessarily reflect the severity of the underlying aortic tissue degeneration [1, 6]. The anatomical type of the valve (pattern of cusp fusion or orientation) and the phenotype of the aorta (pattern of dimensions at different segments) might prove clinically useful markers of risk [7, 8].

†Presented at the 27th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 5–9 October 2013.

© The Author 2014. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery. All rights reserved.
To define valve morphotype, quite simple schemes are currently employed [9]. Conversely, and unlike for aortic dissection, there is no official systematization of the different anatomical forms of aortic dilatation. The ideal classification system should have both a descriptive value and a prognostic potential, i.e. it should identify unique associations of clinical variables and segregate phenotypic groups with different natural course.

The aim of the present study was to test different previously proposed methods for classification of the aortic phenotype in BAV patients in terms of both descriptive meaningfulness and prognostic significance.

MATERIALS AND METHODS

Patients

Since 1998, at our outpatient and perioperative echocardiography service, all transthoracic or transoesophageal echocardiography examinations performed in patients with a BAV (diagnosed either by echocardiography or later on at surgery) have been recorded and the respective clinical data prospectively collected in a database. For the purposes of the present study, for a longitudinal analysis we retrospectively selected patients with serial examinations reaching at least 1 year of follow-up, whereas for a cross-sectional analysis we included both the exams of patients with no follow-up or a total follow-up time of <1 year and the most recent echocardiograms performed in the patients of the longitudinal cohort. The exclusion criteria were: unicuspid aortic valve, associated significant congenital or acquired cardiac diseases (e.g. mild dysfunction of another valve, cardiomyopathies, endocarditis, untreated or recurrent coarctation), aortic dissection, systemic syndromes (Marfan, Loes-Dietz, Ehler-Danlos, Turner etc.) and previous cardiac surgery (except for successful coarctation repair). Thus, 696 patients (mean age 48 ± 16 years, male/female ratio 3:1) were included in the cross-sectional study arm. The study was approved by the local Institutional Review Board.

Variables

Three experienced operators performed all echocardiographic examinations. Aortic stenosis severity was graded by integration of Doppler methods, continuity equation and planimetry; aortic regurgitation degree was defined by composite evaluation of proximal jet width, abdominal aortic Doppler and left ventricular end-diastolic dimension [10]. Predominant aortic stenosis was defined as the degree of stenosis ≥moderate and ≥the degree of regurgitation; predominant regurgitation as degree of regurgitation ≥moderate and exceeding the degree of stenosis. Bicuspidy of the aortic valve was defined by systolic fish-mouth appearance of the orifice in parasternal short-axis views. Only cases with undoubted congenital bicuspid valve morphology were included. Valve morphotype, i.e. the pattern of cusp fusion, was categorized as RL (fusion between right and left coronary cusps), RN (between right and non-coronary cusps) and LN (left and non-coronary) [9]. The aorta was measured at least twice (inner-edge-to-inner-edge method) by bidimensional imaging in parasternal long-axis views, at the root (maximal dilatation of the sinuses of Valsalva), sinotubular junction (STJ) and ascending aorta (at the right pulmonary artery level). When needed, aortic measurements were repeated ‘off-line’ to get full consistency of methods throughout the present study.

Three different phenotypic classifications of the ascending aorta were considered (Fig. 1).

One was based on our previous studies, whereby the morphology of aortic dilatations with both BAV and tricuspid aortic valve (TAV) could be categorized according to the tract predominantly or exclusively involved (sinuses - root vs tubular segment - mid-ascending aorta - ) [4, 7, 11]: we suggested the terms 'root phenotype' and 'ascending phenotype'. The aorta was defined dilated if the ratio of its diameter to the expected normal aortic diameter for the patient’s age and body surface exceeded 1.15 [12]. This threshold corresponded in the present study population to 39 mm on average, that is 2 standard deviations (SDs) above the mean expected root diameter according to Roman’s formulas (34 ± 2.5 mm) [4, 13]. Given the mean bovine serum albumin (BSA) of 1.85 m², the cut-off corresponded to an aortic size index of ≥2.1 cm²/m² [12].

The second classification method, as previously proposed by Schaefer et al. [14], defines the aortic shape, with no need to establish a definition of dilatation, as it considers the mere relations among dimensions: 'N shape' (ascending < sinuses > STJ), 'A shape' (ascending > sinuses > STJ) and 'E shape' (sinuses < STJ), irrespective of ascending tract size.

The third method, a classification scheme mentioned in a surgical study by Park et al. [15] from the Mayo Clinic, based on the criterion of the presence/absence of dilatation at the root and/or ascending tract, identifies, apart from the normal aorta, a ‘type I’ dilatation, located at the ascending tract only, a ‘type II’, involving both the ascending and the root (regardless of which tract shows the greatest dimensions) and a ‘type III’, confined to the root. For this classification, to which we will refer as Park’s classification hereafter, no cut-off was originally suggested for dilatation definition [15]: here, we used the widely adopted criterion of an aortic size index of > 2.1 cm²/m² [12, 16]. A measurement of the most distal part of the ascending aorta and/or proximal horizontal arch was available in ~50% patients. Therefore, we did not take into consideration other proposed classification schemes that would have required measurement of the arch by other imaging modalities (computed tomography (CT) scan, magnetic resonance imaging (MRI))[17, 18].

Other variables considered included hypertension, atherosclerotic disease, chronic obstructive pulmonary disease (COPD), myxomatous and/or prolapsing mitral valve, obesity, ejection fraction, left ventricular end-diastolic diameter (LVEDd) and inter-ventricular septal thickness (IVStd) [4].

Cross-sectional study

The cross-sectional part of the present analysis was undertaken to assess whether the three methods of classification were able to distinguish unique clinical-anatomical phenotypes. Therefore, we searched for significant associations between the anatomical configuration of the aorta and the other abovementioned variables, with particular focus on the valve morphotype (pattern of cusp fusion).

Longitudinal study

Only patients with complete echocardiographic data who had undergone at least two examinations at least 1 year apart, excluding those with LN cusp fusion, were included in the longitudinal
arm of the present study: thus, 150 patients were selected. The aim of the longitudinal analysis was to compare the different aortopathy phenotypes, as defined by three different schemes, in terms of growth rate of the aorta, in order to identify a phenotypic classification method with potential prognostic relevance. Aortic growth rate was defined as the difference between the diameter at last control and the baseline diameter, divided by the follow-up time interval in years. We focused on the ascending tract since in previous studies BAV patients showed the maximal rate of aortic growth at this level [7, 19]. Fast progression was defined as a growth rate at the ascending tract level falling within the top quintile of distribution of the growth rate variable [7, 19].

**Statistical analysis**

Continuous variables were tested for normality of distribution and accordingly summarized as mean ± SD or median [interquartile range (IQR)] and compared between two and more groups through the unpaired t-test and analysis of variance (the latter with the Bonferroni post hoc test) or Mann–Whitney U-test and Kruskal–Wallis test, respectively. Categorical variables were presented as count (percentage) and compared by \(\chi^2\) or (when the expected cell count in a contingency table was <5) Fisher’s exact test. The above tests were also used to identify factors having significant association with a fast growth (fifth quintile) of the ascending aorta in

---

Figure 1: Schematic representation of the spectrum of possible patterns of aortic dimensions observed in association with BAV and their classification according to the three tested methods. The broken lines indicate the profile of a normal proximal aorta. Arrows emphasize the dimensional relations between diameters at the sinus, sinotubular and tubular levels.
univariate analysis: those factors entered as covariates in multivariable logistic regression models, developed by forward stepwise method (stepping criteria: F probability <0.05 for entry, >0.1 for removal) to identify independent predictors of a fast growth. Analysis was performed through the SPSS statistical software (ver16.0); significance level was set at P (two-tailed) <0.05.

RESULTS

Cross-sectional study

Valve morphotype data were available in 626 of 696 (90%) patients: 433 valves had a RL coronary cusp fusion pattern (69.2%), 189 a RN pattern (30.2%) and 4 a LN pattern (0.6%). The LN BAV patients were excluded from the analysis, due to the very low prevalence. The RN type of BAV was associated with smaller mean aortic root dimensions than the RL type, whereas the mean ascending tract diameter was not significantly greater. However, when indexed to the BSA, the ascending tract resulted significantly larger in the RN group (2.4 ± 0.5 cm/m² vs 2.3 ± 0.5 cm/m²; P = 0.022). The most frequent valve status with RL type was normal function (44%), followed by predominant stenosis (30%), and with RN type it was predominant stenosis (48%) followed by predominant regurgitation (33%). A dilatation of the proximal arch and/or distal ascending aorta (data available in 329 patients) was observed in 39% RN patients vs 13% RL (P < 0.0001).

A complete set of proximal aortic measurements was available in 96% of the cases included in the analysis, and thus, Schaefer’s phenotypic class could be defined for 668 patients: there were 176 type N aortas (26%), 399 type A (60%) and 93 type E (14%). The associations between clinical-echocardiographic variables and the three classes N, A and E are depicted in Table 1: apart from the valve morphotype, the three ‘aortic shapes’ showed significant differences in terms of other five variables. When the aortic configuration was defined as the basis of the tract(s) involved by dilatation (‘Park’s classification’), 242 patients were classified as having a normal aorta (35%), 313 a dilatation of the ascending tract (45%), 90 a dilatation of both the ascending and the sinus tracts (13%) and 51 (7%) a dilatation confined to the sinuses. Apart from valve morphology, eight other clinical-echocardiographic variables showed significant differences among the configurations normal, ascending (type I), ascending + root (type II) and root (type III, Table 1). Finally, according to our classification of the aortic phenotypes, 178 patients had a ‘non-dilated’ phenotype (26%), 422 an ‘ascending dilatation’ phenotype (60%) and 96 a ‘root dilatation’ phenotype (14%). The three phenotypes showed significant differences in terms of valve morphotype and eight other variables, among which were higher BSA, larger LVEDd, younger age and aortic regurgitation (Table 1).

The spectrum of different patterns of aortic dimensions possibly observed in association with BAV and their classification according to the three tested methods are shown in Fig. 1.

<table>
<thead>
<tr>
<th>Table 1: An overview of the significant (P &lt; 0.05) univariate associations between phenotypic classes and clinical variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schaefer’s shape</strong></td>
</tr>
<tr>
<td>RN type</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>BSA</td>
</tr>
<tr>
<td>Stenosis</td>
</tr>
<tr>
<td>Regurgitation</td>
</tr>
<tr>
<td>LVEDd</td>
</tr>
<tr>
<td>IVSTd</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

The table reports, for each classification scheme, the class showing the highest prevalence or the highest mean for a given variable (e.g. for RN type: E means that the greatest prevalence of RN type was in patients classified as ‘E shape’ by Schaefer’s method; for age: II means that the group of patients classified as ‘type II’ by Park’s method had oldest mean age). *P < 0.001; -: no significance.

BSA: bovine serum albumin; LVEDd: left ventricular end-diastolic diameter; IVSTd: inter-ventricular septal thickness; COPD: chronic obstructive pulmonary disease.

Longitudinal study

The longitudinal cohort (n = 150) was comparable with the remaining part of the patient population (n = 546) in terms of demographics, anthropometrics, associated conditions, valve morphotypes and aortic phenotypes. As expected, patients with a retrospective follow-up presented less frequently with an at least moderate degree of stenosis (25 vs 35%, P = 0.03) and/or a severe degree of aortic regurgitation (2.7 vs 20%, P < 0.001) and had significantly smaller aortic diameters at the STJ (34 ± 6 mm vs 36 ± 6 mm, P = 0.014) and at the ascending tract (40 ± 8 mm vs 42 ± 9 mm, P = 0.037) compared with those with only one examination.

The mean follow-up time was 4.6 ± 2.7 years (median: 3.6, IQR: 2.5–5.3, range: 1–13 and cumulative: 611 patient-years). No difference was observed among phenotypic classes in terms of the follow-up time length both when employing our classification method (P = 0.61) and by using Schaefer’s (P = 0.26) or Park’s (P = 0.63) methods. The mean growth rate was 0.33 mm/year at the root (median: 0; IQR: [0–0.4]), 0.50 mm/year at the ascending level (median: 0.22, IQR = [0–0.77]). The average total increase in diameter from the first observation to the last follow-up was 0.8 mm at the root, 0.6 mm at the STJ and 2.2 mm at the ascending tract. Figure 2 shows the mean and median yearly changes in ascending aortic diameter for each aortic phenotype group according to the three different methods.

Ascending aorta growth rates fell within the fifth quintile of the variable distribution if >0.96 mm/year: this was therefore the threshold for definition of a fast growth.

The univariate correlates of fast growth of the ascending tract diameter are given in Table 2: of note, although the prevalence of RN morphotype was increased among fast progressors, the difference did not reach statistical significance. No significant differences were observed in terms of baseline aortic diameters between patients with fast progression and those with slower progression (root: P = 0.6; STJ: P = 0.6; ascending: P = 0.13); however, the pattern of dimensions did have an impact (Table 2). In multivariable analysis, only a shorter follow-up and the ‘root phenotype’ emerged as independent predictors of fast growth of the ascending diameter (Table 2).

DISCUSSION

To our knowledge, no other study has ever tested different classification schemes for the description of the aortic phenotype in BAV.
patients. We considered undertaking such an analysis because: (i) disparate classification schemes have been recently used to define the pattern of aortic dimensions in BAV patients [7, 14, 15, 17, 18, 20], after the evidence of a remarkable anatomical and clinical heterogeneity [1-5]; (ii) a phenotypic classification of the BAV aortopathy may stand to reason not only for nosological purposes, but also, if proved to be of prognostic relevance, as a tool for risk stratification. It is currently supposed that a pathogenetical heterogeneity could subserve both the variability in the phenotypic expression and the relative unpredictability of natural history of BAV-related aortic disease. Thus, the phenotype in a broad sense could represent a key to decode the prognosis of the individual BAV patient, thereby guiding a personalized and more insightful medical and surgical management.

Phenotypic classifications of the BAV aorta

Chronologically, our method of classification of the ascending aorta dilatations was the first to be introduced in 2006 [11] and thereafter applied to the BAV population [4]. We postulated, within a theory of possible coexistence of a genetic defect and a haemodynamic pathogenetic factor, that the root phenotype might identify those BAV patients with greater expression of a genetically determined vessel wall weakness and lesser contribution of the mechanics.

As far as descriptiveness is concerned, we confirmed here the previously found association between root phenotype and male sex, younger age, RL morphotype, predominant aortic regurgitation with larger LVEDd compared with the other BAV patients [4, 8].

Also using the classification proposed by Schaefer et al. [14] significant correlations between the aortic valve morphotype and what they defined as the aortic ‘shape’, classified as A, N or E, could be observed. However, being based merely on the pattern of dimensions at the three levels of sinuses, STJ and tubular tract, this method classifies a dilated aortic root with normal or less dilated ascending tract as N just as a normal aorta, in which usually the root diameter exceeds the tubular dimension (Fig. 1). Others [20] have modified the criteria for shape definition, by introducing a cut-off (40 mm) to define the presence of dilatation and therefore indicating as N the non-dilated aorta, as A and E, respectively, the dilated aorta without and with effaced STJ. However, after this modification no association with valve morphotype emerged anymore [20], and thus, the comprehensive nature of Schaefer’s classification [14] was at least in part frustrated.

Park et al. [15], when proposing their classification, failed to acknowledge the prevalence, features and outcomes of the individual dilatation types in their series; however, another group has recently reported significant association of the RN BAV with type I dilatation and of RL BAV with type II [13]. In summary, all three compared methods might represent well-comprehensive descriptions of the anatomy of both valve and aorta; nevertheless, we observed a greater descriptive potential of Park’s and our method (association with a greater number of variables and higher levels of significance), in cross-sectional analysis, compared with Schaefer’s one (Table 1).

Other proposed classification schemes [17, 18] take into account also the dimensions of the aortic arch and therefore require CT scan or MRI for phenotypic definition. The issue of associated arch dilatation in BAV disease, underscored in a small uncontrolled series [18], is interesting in research; however, its clinical relevance has been more recently downsized by the evidence, from larger BAV series with TAV controls, that the arch is spared by the aortopathy in most cases [21].

Regarding the prognostic implications, it is worthy of consideration that each phenotypic classification implies some loss of information (presence/absence of dilatation, in Schaefer’s system; level of maximal dilatation, in Park’s method; dilatation confined to one segment vs prevailing at one segment, in our classification): which of these pieces of information is related to the underlying severity of the aortopathy and therefore holds prognostic meaning? Our results suggest that the presence and level of maximal dilatation

---

**Figure 2:** Differences in mean and median growth rates in different subgroups of BAV patients distinguished according to the three classification schemes. Light bars represent mean growth rate (±standard error of the mean) at the tubular ascending tract, dark bars represent the median values.
## Table 2: Longitudinal study: univariate correlates and multivariable predictors of fast ascending aorta diameter progression over time in BAV patients (n = 150; column percentages presented)

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th>Multivariable analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast progressors (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-fast progressors (n = 118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>Odds ratio</td>
<td>95% CI</td>
<td>P-value</td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43 ± 15</td>
<td>45 ± 16</td>
<td>0.47</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>7 (21%)</td>
<td>31 (26%)</td>
<td>0.70</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valve morphotype (RN)</td>
<td>14 (42%)</td>
<td>32 (27%)</td>
<td>0.09</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Regurgitation (≥ moderate)</td>
<td>15 (47%)</td>
<td>33 (28%)</td>
<td>0.048</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stenosis (≥ moderate)</td>
<td>9 (28%)</td>
<td>28 (24%)</td>
<td>0.80</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (12%)</td>
<td>2 (17%)</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (9%)</td>
<td>16 (14%)</td>
<td>0.77</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aortic root diameter (mm)</td>
<td>36 ± 6</td>
<td>36 ± 6</td>
<td>0.60</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>STJ diameter (mm)</td>
<td>33 ± 8</td>
<td>34 ± 8</td>
<td>0.62</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ascending diameter (mm)</td>
<td>39 ± 8</td>
<td>41 ± 8</td>
<td>0.13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aortic phenotype [4]</td>
<td>0.005</td>
<td>4.5</td>
<td>1.4–17</td>
<td>0.009</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-dilated</td>
<td>8 (25%)</td>
<td>40 (34%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ascending</td>
<td>13 (40%)</td>
<td>67 (57%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Root</td>
<td>11 (34%)</td>
<td>11 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aortic shape [14]</td>
<td>0.055</td>
<td>-</td>
<td>-</td>
<td>0.60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>N</td>
<td>17 (53%)</td>
<td>35 (30%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A</td>
<td>9 (28%)</td>
<td>60 (51%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>6 (19%)</td>
<td>23 (19%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dilatation type [15]</td>
<td>0.42</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>None</td>
<td>15 (47%)</td>
<td>47 (40%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type I</td>
<td>9 (28%)</td>
<td>36 (31%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type II</td>
<td>6 (19%)</td>
<td>31 (26%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type III</td>
<td>2 (6%)</td>
<td>4 (3%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>3.9 ± 1</td>
<td>4.8 ± 2</td>
<td>&lt;0.001</td>
<td>0.4</td>
<td>0.2–0.9</td>
<td>0.004</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; STJ: sinotubular junction.
might be related to the prognosis, at least in terms of rapidity of dilatation progression over time: this was faster with the root phenotype, consistent with a greater severity of the aortopathy. Confirming this hypothesis, an independent surgical series of isolated aortic valve replacement recently showed that, compared with patients with BAV stenosis and ascending phenotype, those with the root phenotype had a lower freedom from adverse aortic events in the postoperative follow-up [5].

Clinical implications

The scientific bases on which the current surgical approach to BAV aortopathy rely are increasingly being object of criticism [1–3]. The dominant trend favours a higher level of aggressiveness in posing the indication to aorta resection in BAV patients than in TAV counterparts, and in a recent large series of proactive surgery of the ascending aorta, 20% patients had a maximal diameter ≤41 mm [22]. In contrast, others have reported series in which the cut-off for BAV-related aortopathy treatment was as high as 50 mm even in patients undergoing aortic valve replacement [5]. Those policies represent the extremes of a wide range of different practices: a recent survey has demonstrated that many surgeons’ attitudes towards BAV aortopathy are based on arbitrary concepts or institutional policies rather than being supported by guidelines [16]. Such disparities in surgical practice at least in part derive from a lack of knowledge of the prognostic significance of phenotypic differences [16]. Improved phenotypic stratification of BAV patients may lead to a more rational general surgical posture, through personalization of indications.

The evidence from the present investigation, although warranting further confirmation in larger longitudinal studies, clearly suggests that a more aggressive surgical approach (i.e. earlier indication, more extensive resection) would be justified when treating root phenotype patients, compared with the other BAV patients. Notably, since we considered the growth rates at the ascending tubular segment, our results imply that the natural progression of the root phenotype also includes distal propagation of the dilatation. Moreover, a possible practical implication arising from the present result is that clinical surveillance should be probably stricter (i.e. more frequent echocardiographic and/or CT controls) also in BAV subjects with non-dilated aorta but with characteristic features typical of the root phenotype [4]. On the other hand, the majority of BAV aortopathy patients, presenting an ascending phenotype, show a typically indolent progression (Fig. 2), with a median growth rate of 0.22 mm/year (mean 0.4 mm/year), 10 times lower than the cut-off for surgical indication suggested by the recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines [23]. The median growth rate at the sinus level was 0 in this group (mean 0.2 mm/year), supporting the opinion that a proactive Bentall operation is not needed, i.e. if the root is not already distinctly dilated in this subset of patients [15], also considering that they are generally older at operation than root phenotype patients [11].

Limitations of the study

This descriptive study was not population-based, and therefore, it suffered from the common limitations of retrospective, outpatient-based studies performed at secondary and tertiary referral centres. In particular, in the longitudinal arm of the study, we focused on the aortic growth rather than on aortic events, because the latter were biased by the retrospective design and referral pattern (as we included in the echocardiographic database also a proportion of patients being diagnosed BAV at surgical inspection, so the event itself was rather the channel of enrolment than an outcome measure). However, growth rates, which constituted the focus of the longitudinal analysis, were not influenced by this bias and are currently considered good surrogate metrics for the severity of the aortopathy [19, 23]. Both validation of the present results in larger independent cohorts and additional studies prospectively assessing the rates of aortic events or surgery in the individual phenotypes are warranted. The lack of measurements of the more distal segments of the aorta must also be acknowledged (measures available in 352 patients, 23 of which had no definition of the valve morphotype), this limitation being inherent in the echocardiographic method. Finally, a comprehensive phenotypic stratification could possibly include further details that we have decided to omit in this analysis, e.g. the presence/absence of a raphe in the fused cusp: however, this allowed comparison with Schaefer’s classification, as that author considered BAVs with and without raphe in the same morphotype groups as well [14].

Conclusions

All three previously proposed echocardiographic classification methods for the aortic phenotype in BAV patients proved satisfactorily comprehensive in terms of descriptive meaningfulness in cross-sectional analysis. In longitudinal, only our own method discriminated a subgroup of patients (those with root phenotype) with significantly worse evolutivity of the dilatation.

If confirmed in prospective natural-history studies, the phenotypic class of the aorta (non-dilated, ascending and root phenotypes) could be a factor to integrate in future comprehensive models for risk stratification of BAV aortopathy, possibly along with circulating biomarkers and functional imaging parameters, such as aortic wall elastic properties [10], valve cusp kinematics [24] and flow features [25]. It can be anticipated that knowledge improvements and the availability of risk stratification tools will eventually have a tremendous impact on surgical practice guidelines.

Funding

This work was supported by a ‘Ricerca Finalizzata’ grant from the Italian Ministry of Health (GR09-1580434) to Alessandro Della Corte.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr M. Grabenwöger (Vienna, Austria): I have heard in this session today a lot of classifications with respect to bicuspid aortiic valves, and I have to confess in the meanwhile that I’m really a little bit confused. We have different classifications concerning the morphology of the leaflets and we have different classifications concerning the morphology of the root, sinus of Valsalva, sinotubular junction, and ascending aorta. And here you showed us three different kinds of classifications. My proposal would be to constitute a European working group to say “this is the best one”. Because for those of us who are, for example, not real experts in aortic valve practice, it is confusing to have three different classification methods.

If I followed you correctly, the root type has the worst prognosis where you have a dilatation of the sinus of Valsalva. Ultimately, if you have these three classifications in mind and the knowledge that the root type has the worst prognosis, how does this influence your daily practice when you have to operate on a patient with a bicuspid valve? We know in general you have to be more aggressive if you have a bicuspid valve. We know the connective tissue of the ascending aorta is different to a tricuspid valve, but additional information gives us the exact classification.

Dr Della Corte: You are absolutely right about the confusion that is created by the existence of different classification schemes for both valve type and for aortic phenotype. And this is one of the reasons why we have undertaken this type of study to try to find an agreement on a common terminology in this field.

With regard to practice, I think that if confirmed in a prospective, and possibly multicentre design, as you suggest, not only patients who present with the root phenotype may be treated more aggressively, but also patients who have the clinical features of the root phenotype: these are usually younger patients, only male patients, almost no female patients in this group; they usually develop aortic regurgitation as a predominant valve dysfunction; they do not show asymmetry of the dilatation in 3D imaging methods; they are also taller than the other ones, in this situation that resembles a Marfan-like syndrome, let’s say. However, they are only 15%–20% of the whole bicuspid aortic valve population. So I think in the remaining patients we will find other risk markers that will help us further stratify the BAV population.

Dr G. Thieme (Padua, Italy): Listen, I like to use the term sinus versus tubular aortic phenotype. To my mind, as a pathologist, it sounds better. Which of the two is at more at risk of dissection? I surmise it is the tubular one. Is it?

Dr Della Corte: In general the most frequent type of entry tear in dissections is the tubular tract, both in tricuspid and bicuspid aortic valve patients. We saw a presentation by Dr Etz from Leipzig on this yesterday. However, the prevalence of cases with entry tear at the root, although they are a minority, is higher with bicuspid than with tricuspid aortic valves. And I suspect that those can be patients with the root phenotype.

Dr J. Bachet (Nogent-sur-Marne, France): We have heard a lot of papers this morning about the aorta and bicuspid valve. But let’s go back to the real world. Patients with bicuspid valve are sent to the surgeon not because of the aorta, but because of the valve. And some of them have an aortic problem. So, although what you said is extremely interesting intellectually, practically when we see a patient that needs an aortic valve replacement because of his bicuspid valve and we see that the aorta is dilated more than 45 mm, whatever the phenotype is, we replace the ascending aorta. And if he has a root dilatation, we have to do a root replacement. So the phenotype has no influence, in my opinion, on the practice of surgery. And I suspect that if in your statistics the root phenotype had a worse evolution than the other phenotype, it’s not because it’s very different, it’s possibly because many surgeons facing a root dilatation are not replacing the root, so they get into trouble.

Dr Della Corte: Well, my analysis was only on the preoperational natural history. There is no postoperative follow-up in my study. Others, the group from Bad Berka, have studied the follow-up after simple AVR when leaving a 5 cm aorta untreated. And I agree those patients must have a worse prognosis because no one has treated the root and the ascending aorta with a Bentall operation, for example.

But I think this evidence may be useful also for surveillance purposes, not only for surgery, and for possible medical therapy emerging in the future.